Bayer

Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-9741
Phone: 412 777-2000

May 3, 2001

Christine Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

Dear Administrator Whitman;

Bayer Corporation is pleased to submit the proposed test plan along with the current robust summaries in IUCLID format for cyclohexyl isocyanate (CAS# 3173-53-3). All documents are Adobe Acrobat (pdf) files.

We will not begin animal testing until the comment period has expired and we have time to review submitted remarks.

Bayer Corporation's registration number is . Cynthia Graham, Ph.D. is our technical contact and can be reached at 412-777-3933 or by email at cynthia.graham.b@bayer.com

Sincerely,

Donald W. Lamb, Ph.D.
Vice President
Product Safety & Regulatory Affairs

Enclosures: Test Plan, IUCLID data set on CAS# 3173-53-3

cc: H.H. Wehmeier

Cyclohexyl isocyanate

CAS # 3173-53-3

Test plan justification

Cyclohexyl isocyanate reacts with substances which contain active H atoms, such as water, acids, alkaline solutions, ammonia, primary and secondary amines, alcohols, mercaptans,and phenols. A reaction with water causes CO_2 to split off and symmetrical di-cyclohexyl urea to form, amongst other products. Catalytically acting compounds such as tertiary amines, phosphines, some metals and metal salts can cause cyclohexyl isocyanate to react with itself, forming dimers and trimers. During processing, CHI reacts completely (usually with amines) to create the desired product.

Because of the exceptional reactivity of CHI, there are strict operating procedures for production, storage, transport, and processing including the use of closed apparatus and fixed pipelines constructed of specific materials.

Cyclohexyl isocyanate is stored under controlled conditions and there is limited, controlled transport. It is therefore classified as a “closed system intermediate”. In this regard, limited testing is required: no Repeat dose toxicity or Reproductive Toxicity testing is warranted.

Physicochemical properties:
The properties of cyclohexyl isocyanate can be found in Handbooks such as CRC Handbook of Chemistry and Physics and have been documented by Bayer AG. Although original documents are not available for all endpoints, no additional testing is proposed. (See attached IUCLID document)

Environmental Fate:
Photodegradation and Fugacity were modeled using the EPIWIN Program , as recommended by the HPV Challenge Guidance. An OECD Guideline study of biodegradation was performed on cyclohexyl isocyanate, and summarized in the attached UCLID document.

The rapid hydrolysis of isocyanates in water is known, however no study was located on cyclohexyl isocyanate. It is proposed to determine the rate of hydrolysis along with degradation products of cyclohexyl isocyanate using OECD 111. This data will also aid in the ecotoxicity endpoints.

Ecotoxicology:
Isocyanates are believed to hydrolyze to the associated amine (i.e. cyclohexylamine). The OECD 111 study will confirm the degradation product. Since there are many studies on fish, Daphnia and algae using cyclohexylamine, it is believed that these endpoints will be filled with that data. No additional testing is proposed if cyclohexylamine is the rapid degradation product of cyclohexyl isocyanate in water.

Mammalian Toxicology:
There are two well documented studies on acute oral, inhalation and dermal toxicity, as summarized in the attached IUCLID.

Cyclohexyl isocyanate is a “closed system intermediate” because each of the uses is to undergo a deliberate reaction to create another substance. Cyclohexyl isocyanate is stored under controlled conditions and there is limited controlled transport. In this regard, limited testing is required. Therefore no Repeat dose toxicity or Reproductive Toxicity testing is warranted.

There are no studies to fill the Mutagenicity endpoints, therefore OECD 471 and 473 are proposed.

To fulfill the Developmental Toxicity endpoint, required even though there is limited exposure due to the chemical being an intermediate, OECD 414 is proposed.

Table 1. Test Plan for Cyclohexlisocyanate

Endpoint	Data Availability	Acceptable	Planned testing
Physical-Chemical Data			
Melting Point	-80 C	✓	
Boiling Point	172 C	✓	
Vapour Pressure	2.2 hPa @ 20 C	✓	
Partition Coefficient ($logP_{ow}$)	Not determinable - hydrolysis	✓	
Water Solubility	hydrolysis	✓	
Environmental Fate			
Photodegradation	EPIWIN	✓	
Fugacity	EPIWIN	✓	
Biodegradability	✓	✓	
Water Stability			OECD 111
Ecotoxicology			
Acute Fish Toxicity	**Only LC_0**		Use CHA data*
Acute Invertebrate Toxicity			Use CHA data*
Algal Toxicity			Use CHA data*
Mammalian Toxicology			
Acute Toxicity	✓	✓	
Mutagenicity			OECD 471
Chromosome Aberration			OECD 473
Repeated Dose Toxicity			Intermediate- no testing necessary
Reproductive Toxicity			Intermediate- no testing necessary
Developmental Toxicity			OECD 414

✓ = data available and considered adequate.

* The Water Stability study will determine degradation products, believed to be cyclohexylamine (CHA). CHA has adequate data for these endpoints

I U C L I D

D a t a S e t

Existing Chemical	ID: 3173-53-3
CAS No.	3173-53-3
EINECS Name	cyclohexyl isocyanate
EINECS No.	221-639-3
Molecular Formula	C7H11NO
Molecular Weight	125.17

Producer Related Part	
Company:	Bayer Corporation
Creation date:	15-JUL-1999
Substance Related Part	
Company:	Bayer Corporation
Creation date:	15-JUL-1999
Memo:	Bayer Corporation
Printing date:	23-APR-2001
Revision date:	
Date of last Update:	23-APR-2001
Number of Pages:	9
Chapter (profile):	Chapter: 2.1, 2.2, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.5, 4.1, 4.2, 4.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.8, 5.9
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

2.1 Melting Point

Value: -80 degree C
Method: other: historical data
Testsubstance: other TS: cyclohexylisocyanate
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

2.2 Boiling Point

Value: 172 degree C at 1013 hPa
Method: other: Handbook value
Testsubstance: other TS: cyclohexylisocyanate; purity not noted
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-APR-2001 (2)

2.4 Vapour Pressure

Value: 2.2 hPa at 20 degree C
Method: other (measured): historical data
Testsubstance: other TS: cyclohexylisocyanate
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

Value: 12 hPa at 50 degree C
Method: other (measured): historical data
Testsubstance: other TS: cyclohexylisocyanate
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

2.5 Partition Coefficient

log Pow:
Method:
Year:
Testsubstance: other TS: cyclohexylisocyanate
Remark: A log Pow is not determinable due to the instability in water.
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

2.6.1 Water Solubility

Qualitative: other: rapid hydrolysis
Testsubstance: other TS: cyclohexylisocyanate
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1560000 molecule/cm3
Rate constant: .00000000001 cm3/(molecule * sec)
Degradation: 50 % after 12.8 hour(s)
Method: other (calculated): AOP Program (v1.89)
Year: GLP: no
Test substance: other TS: molecular structure
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (3)

3.1.2 Stability in Water

Type:
Method:
Year: GLP:
Test substance:
Remark: Hydrolysis !
Flag: Critical study for SIDS endpoint
23-APR-2001 (1)

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other: air, water, soil, sediment
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other: EPIWIN Level III Fugacity Model
Year: 1999
Result:

	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	7.03	25.7	1000	8.77e-011
Water	31	360	1000	1.33e-008
Soil	61.6	360	1000	2.53e-008
Sediment	0.365	1.44e+003	0	6.37e-009

Persistence Time: 213 hr
Reaction Time: 272 hr
Advection Time: 987 hr
Percent Reacted: 78.4
Percent Advected: 21.6
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (3)

3.5 Biodegradation

Type:	aerobic
Inoculum:	predominantly domestic sewage
Concentration:	.8 mg/l
Degradation:	75 % after 20 day
Method:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year:	1979 GLP: no
Test substance:	other TS: purity: approx. 98 %
Remark:	1 g/l Emulgator W (CAS-No. 68130-72-3) used as emulsifier
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

23-APR-2001 (1)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type:	static
Species:	Leuciscus idus (Fish, fresh water)
Exposure period:	72 hour(s)
Unit:	mg/l Analytical monitoring: no
LC0:	.5
Method:	other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische. DEV, L 15 (1979)
Year:	1979 GLP: no
Test substance:	other TS: purity: approx. 98 %
Remark:	range finding test
Flag:	Critical study for SIDS endpoint

23-APR-2001 (1)

4.2 Acute Toxicity to Aquatic Invertebrates

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4.3 Toxicity to Aquatic Plants e.g. Algae

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5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Strain:	Sprague-Dawley
Sex:	male/female
Number of Animals:	20
Vehicle:	other: undiluted
Value:	560 mg/kg bw
Method:	
Year:	1974 GLP: no data
Test substance:	other TS: cyclohexyl isocyanate; purity not noted
Method:	The undiluted compound was fed by stomach tube to Sprague-Dawley albino male and female rats. After the approximate Minimal Lethal Dose was determined, groups of male and female rats were fed in increasing doses at increments of 0.1 fractional log intervals at four levels to cover the toxicity range. The data was used to calculate LD50 by the method of EJ de Beer. Observations were made for toxic signs over a 14 day period and the viscera of the animals were examined macroscopically.
Result:	The single oral dose LD50 for male and female rats was placed at 560mg/kg bw with lower and upper limits of 490 to 630 mg/kg bw. Toxic signs included reduced appetite and activity (1-3 days in survivors), increasing weakness, collapse, and death. Survival time was several hours to 2 days. Autopsy findings were lung and liver hyperemia, and acute gastrointestinal inflammation. Surviving animals were sacrificed 14 days afer dosing. The viscera appeared normal by macroscopic examination.
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

23-APR-2001 (4)

Type:	LD50
Species:	rat
Strain:	Sprague-Dawley
Sex:	male/female
Number of Animals:	4
Vehicle:	other: 20% ethanol-80% propylene glycol solution
Value:	335 - 625 mg/kg bw
Method:	other
Year:	1974 GLP: no data
Test substance:	other TS: cyclohexyl isocyanate; purity = technical grade
Method:	Male Sprague-Dawley rats (weighing 270-300g) and females (weighing 200-250g) were fasted for 24 hours before the compound was administered. The compound was diluted so that each animal received its dose in a volume equivalent to 0.1-0.2% body weight. Graded doses were given to four groups of 4 animals by gavage. Symptoms and mortality were recorded for 14 days and the LD50 calculated by the method

of Weil (CS Weil, 1952. Biometrics. 8:349).
Result: LD50 = 625 mg/kg bw (females) LD 50 = 335 mg/kg bw (males)

Rats exhibited symptoms of lethargy and, depending on dose, proceeded to profound sedation.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (5)

5.1.2 Acute Inhalation Toxicity

Type: LC100
Species: rat
Strain:
Sex: male
Number of Animals: 6
Vehicle: other: undiluted
Exposure time: 2.5 hour(s)
Value: ca. 7160 mg/m³
Method:
Year: GLP: no data
Test substance: other TS: cyclohexyl isocyanate; purity not noted
Method: Six mature male rats were placed in a stainless steel chamber of 35 liter capacity and exposed to a concentrated atmosphere of vapors produced by passing a stream of air through 42.4g of the compound contained in a 500ml Erlenmeyer flask. Vapors from the flask were passed though a one liter bottle to remove droplets and then into the chamber. Air flow through the chamber was 4.0 liter/min as measured by a calibrated rotameter. No supplementary air was introduced. The animals were observed for behavior until all succumbed. The viscera of the animals was examined macroscopically.
Result: All six animals succumbed within 2.5 hours after start of exposure. Ocular discharge, labored breathing, and slight lethargy were observed during the first hour of exposure. During 1-2.5 hours of exposure, the animals exhibited increased weakness, collapse and death. Hemorrhagic lungs were seen upon autopsy. Average concentration of the vapors in the chamber was calculated to be 7.16g/m3 (1393 ppm).
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (4)

Type:	LC100
Species:	rat
Strain:	
Sex:	male/female
Number of Animals:	8
Vehicle:	other: undiluted
Exposure time:	2 hour(s)
Value:	ca. 13523.76 mg/m³
Method:	
Year:	GLP: no data
Test substance:	other TS: cyclohexyl isocyanate; purity = technical grade
Method:	The rats were supported on a wire mesh rack inside a 20 liter chamber equipped with a window and exposed to an atmosphere saturated with the test substance. Vapors were generated by passing a stream of air over a known quantity of test material. The air flow was measured by a calibrated flowmeter. Animals were observed until both succumbed.
Result:	Exposure of rats to a saturated vapor of the compound caused noticable eye irritation, dyspnea, salivation, piloerection, and death to all animals exposed. Death occurred within 2 hours. Calculated exposure concentration was approximately 2631.5 ppm (13523.76 mg/m3).
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

23-APR-2001 (5)

5.1.3 Acute Dermal Toxicity

Type:	other: MLD
Species:	rabbit
Strain:	
Sex:	male/female
Number of Animals:	5
Vehicle:	other: undiluted
Value:	2000 - 3160 mg/kg bw
Method:	
Year:	GLP: no data
Test substance:	other TS: cyclohexyl isocyanate; purity not noted
Method:	The undiluted compound was applied in increasing doses at increments of 0.2 fractional log intervals to the closely clipped, intact skin of New Zealand albino male and female rabbits. The treated areas were covered with plastic strips and the animals held in wooden stocks for periods up to 24 hours, after which they were assigned to individual cages. Observations were made for toxic signs over a 14 day period and the viscera of the test animals were examined macroscopically.
Result:	The acute skin absorption Minimal Lethal Dose for male and female rabbits was found to be greater than 2000 and less than 3160 mg/kg bw. Toxic signs included reduced appetite and activity (2-4 days in the survivors), increasing weakness, collapse and death. Survival at the higher doses

was less than 24 hours. Autopsy findings were hemorrhagic lungs, slight liver discloration and gastrointestinal inflammation. Surviving animals were sacrificed 14 days after dosing. The viscera appeared normal by macroscopic examination.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (4)

Type: other: MLD
Species: rabbit
Strain:
Sex: male/female
Number of Animals: 4
Vehicle: other: undiluted
Value: 500 mg/kg bw
Method: other
Year: 1974 GLP: no data
Test substance: other TS: cyclohexyl isocyanate; purity = technical grade
Method: Male and female New Zealand white rabbits (weighing 2-3 kg) were exposed to undiluted compound on their shaved backs for 24 hours, after which the compound was removed. Doses were 200, 500, 1000, 2000 mg/kg bw. Symptoms and mortality were recorded for 14 days.
Result: Minimal Lethal Dose = 500 mg/kg bw
The only obvious symptom was tachypnea.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
23-APR-2001 (5)

5.1.4 Acute Toxicity, other Routes
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5.4 Repeated Dose Toxicity
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5.5 Genetic Toxicity 'in Vitro'
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5.6 Genetic Toxicity 'in Vivo'
-

5.8 Toxicity to Reproduction
-

5.9 Developmental Toxicity/Teratogenicity
-

(1) Bayer AG data

(2) CRC Handbook of Chemistry and Physics. 80th edition (1999-2000) David R. Lide, ed. CRC Press, New York. p 3-123 No. 4416.

(3) Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

(4) Younger Laboratories Study # 9495YLR74 (unpublished)

(5) Chemagro Study #40870 (unpublished)